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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/852,968	CHAN, EUGENE Y.	
	Examiner	Art Unit	
	Stephanie K. Mummert, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,115-122,124,130-156 and 161-169* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,115-122,124,130-156 and 161-169* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on April 23, 2007 is acknowledged and has been entered. Claims 1, 115, 131, 137, 142, 147, 162 have been amended. Claims 3-114, 123, 125-129, 157-160 have been canceled. Claims 1-2, 115-122, 124, 130-156, 161-169 are pending.

Claims 1-2, 115-122, 124, 130-156, 161-169 are discussed in this Office action.

1. Applicant's arguments, see p. 9-11, filed April 23, 2007, with respect to the rejections under 35 U.S.C. 102 as being anticipated by Yeung, Huang and/or Mank have been fully considered and are persuasive. The grounds of rejection have been withdrawn.

All of the remaining amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

PREVIOUS REJECTIONS

The rejection of claims 1-2, 115, 119, 120 under obviousness-type double patenting is withdrawn in view of Applicant's terminal disclaimer, filed May 15, 2007.

The rejection of claims 1-2, 130-133, 135-142, 144-146, 149-152, 154-156, 161-165 and 167-169 under 35 U.S.C. 102(b) as being anticipated by Yeung is withdrawn in view of Applicant's amendment to the claims and attached arguments. The rejection of claims 1-2, 115, 116, 119-124, 130-134, 137-143, 147-153 and 161 under 35 U.S.C. 102(b) as being anticipated by Huang is withdrawn in view of Applicant's amendment to the claims and attached arguments. The rejection of claims 115, 117, 118 and 166 under 35 U.S.C. 102b as being anticipated by Mank is withdrawn in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2, 115-122, 124, 130-156, 161-169 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabling for the labeling of individual units in a polymer for determining the identity of each individual unit sequentially via linear analysis through a nanochannel. The specification also, does not particularly show how to apply the method to polymers that are outside of the protein/peptide and nucleic acid scope of the invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims 1-2 are directed to a method for identifying individual units of a polymer, comprising moving a polymer linearly past a detection point and determining the identity of individual units by detecting a non-ion conductance signal through exposure of linked adjacemt signal generating units. Claims 115-122 and 124 are directed to a method for characterizing a test polymer, comprising linked units that are sequentially exposed to an interaction station. Claims 130-146 are directed to a method of determining order of units of polymers labeled with a light emissive compound and polymer dependent impulses are measured as the units of the polymer linearly pass a station. Claims 147-156 and 161 are directed to a method for analyzing a set of polymers of linked units, orienting the polymers in an electric field and moving the sets of polymers through defined channels including nanochannels. Claims 162-164 are directed to a method of identifying a marker attached to a polymer by detecting signals generated by individual labeled unit specific markers as distinguished over exposure of linked adjacent units of a single polymer. The invention is in a class of invention which the CAFC has characterized

as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method directed to the identification of the specific units of a polymer, comprising moving the polymer releative to a 'station', obtaining polymer-dependent impulses or signals and determining the identity of the units based on the signal generated. Furthermore, the claims encompass any type of polymer, including proteins, nucleic acid, polysaccharides and synthetic polymers.

Quantity of Experimentation and Guidance in the Specification

The quantity of experimentation in this area is large. Regarding the specific polymers analyzed using the method of the instant invention, the specification broadly defines 'polymer' as follows: "A 'polymer' as used herein is a compound having a linear backbone of individual units which are linked together by linkages." And "In a preferred embodiment the polymers are homogeneous in backbone composition and are, for example, nucleic acids, polypeptides, polysaccharides, carbohydrates, polyurethanes, polycarbonates, polyureas, polyethyleneimines, polyarylene sulfides, polysiloxanes, polyimides, polyacetates, polyamides, polyesters, or polythioesters. In the most preferred embodiments, the polymer is a nucleic acid or a polypeptide. A "nucleic acid" as used herein is a biopolymer comprised of nucleotides, such as deoxyribose nucleic acid (DNA) or ribose nucleic acid (RNA). A polypeptide as used herein is a biopolymer comprised of linked amino acids" (paragraph 151 of PgPub). However, the

specification provides no teaching of how to practice the method on polymers that do not comprise either nucleic acids or polypeptides.

Regarding the potential for labeling of each individual unit of a polymer such as a nucleic acid, either extrisically or intrinsically, the specification states that labeling steps which require "that all four bases in the DNA be tagged with different fluorophores" would be "extremely unfavorable" due to steric hindrance (p.2, paragraph 16 of PgPub). Regarding four-color labeling schemes, the specification states "A four nucleotide labeling scheme can be created where the A's, C's, G's, and T's of a target DNA is labeled with different labels. Such a molecule, upon traversing an interaction station, will generate a linear order of signals which correspond to the linear sequence of nucleotides on the target DNA" (paragraph 266 of PgPub). The specification also states that some of the nucleotides may be intrinsically labeled to reduce steric hindrance and states "It is also preferred that when extrinsic labels are used with the four nucleotide labeling scheme that the labels be small and neutral in charge to reduce steric hindrance" (paragraph 266 of PgPub). Clearly, there would be a high degree of experimentation necessary to overcome the issue of steric hindrance in order to incorporate a light emissive compound for each unit of the polymer, particularly in embodiments wherein the polymer is DNA.

Furthermore, the specification does not clearly define the practice of identifying the specific units through intrinsic label(s) that distinguish individual units of a polymer, without using ion conductance measurements. For example, the specification states "The polymer or at least one unit thereof is in a form which is capable of interacting with an agent or station to produce a signal characteristic of that interaction. The unit of a polymer which is capable of

undergoing such an interaction is said to be labeled. If a unit of a polymer can undergo that interaction to produce a characteristic signal, then the polymer is said to be intrinsically labeled. It is not necessary that an extrinsic label be added to the polymer" (paragraph 157 of PgPub). The specification teaches broadly that "Many naturally occurring units of a polymer are light emitting compounds or quenchers. For instance, nucleotides of native nucleic acid molecules have distinct absorption spectra, e.g., A, G, T, C, and U have absorption maximums at 259 nm, 252 nm, 267 nm, 271 nm, and 258 nm respectively" (paragraph 158 of PgPub). While the specification provides an example of a means of 'intrinsic' labeling of nucleic acids, there is no corresponding intrinsic property of amino acids provided which would serve as an 'intrinsic' label for the practice of the invention. Therefore, for the practice of the invention for polymers that do not comprise nucleic acid, there would be a high degree of experimentation necessary to identify intrinsic labels for individual units of additional polymers, including proteins, polysaccharides, carbohydrates and additional synthetic polymers.

Furthermore, while he specification provides multiple labeling schemes (four color, three color, two color) incorporating both intrinsic and extrinsic labels, the specification does not clearly provide specific embodiments wherein a specific 'agent' present at the interaction station of the method of the invention is set to interact with a specific type(s) of label, both intrinsic and extrinsic and provides a measurable result. A variety of options are provided for the interaction, including the specific types of labels that are present in a nucleic acid or protein polymer, and includes a variety of 'agent' formats including electromagnetic radiation, a quenching source and a fluorescence excitation source (paragraph 31) and a variety of label formats including intrinsic labels (inherent features of purine versus pyrimidine nucleotides, for example) and extrinsic

labels including fluorophores or radioactivity (paragraph 56). However, with these disparate and broad teachings, there would be a high degree of experimentation necessary to establish the specific and detailed process of building the specific apparatus necessary for the practice of the invention and establishing the method of identifying and distinguishing individual units of intrinsically labeled and linked nucleotide units in a sequential manner - in addition to providing results for units that are labeled in a more conventional extrinsic manner.

Regarding the formation of the nanochannel pores and their application to the practice of determining the sequence of individual units of a polymer through linear analysis, Applicant has given no indication that such an apparatus or device, comprising nanochannels or a nanoplate has been reduced to practice. A post-filing reference, Chan (Chan, Eugene, Mutation Research, 2005, 573, p. 13-40) notes that "a single-base resolution strategy has yet to be articulated with solid-state nanopores" (p. 30 col. 2 to p. 31 col. 1). The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. While Applicant describes the essential features of such an apparatus in the specification, the fabrication of such a device is not described in the specification in such detail as to obviate undue experimentation by one of ordinary skill in the art. The following paragraph discusses some features of the apparatus required to practice the claimed methods that are unpredictable and would therefore require undue experimentation for reduction to practice.

The unpredictability of the art and the state of the prior art

The current state of the art indicates that a great deal of further experimentation and inventiveness would be required to implement the methods claimed by Applicant.

Regarding the practice of the method of claims 1, 2 and 147-148 using a nanochannel, Applicant in a post-filing reference, (Chan, EY, 2005, 573, p. 13-40) notes that "work in the field of nanopore sequencing has focused on the development of solid-state nanopores that may bypass some of the inherent limitations of protein pores. For instance the use of solid state nanopores allows the use of denaturing conditions suitable for single-stranded DNA." Chan also notes "these nanopores have been used effectively to analyze DNA conformations, and mediate DNA transport with single-base pair mismatch selectivity". However, Chan also notes that "resolution remains an issue for these methods; it is challenging to fabricate a robust nanopore that is less that 3.4 Å in length, the interbase distance. A single-base pair resolution strategy has yet to be articulated with solid-state nanopores" (p. 30, col. 2).

For instance, regarding the issue of providing a 'signal generating unit' for each unit, including through labeling individual units within a polymer, Sauer et al. (Journal of Biotechnology, 2001, 86, p. 181-201) expressly teach that "A complete labeling (100% substitution with fluorescent dNTPs) of all four DNA-bases has not yet to be achieved (sic). Steric hindrance at the polymerase active site is supposed to prevent full replacement of natural dNTPs by the modified analogues (see page 188, column 2)." Since the current specification lacks guidance on how to overcome this art recognized problem, and also notes that the labeling of each individual unit with an 'extrinsic label' such as a light emissive compound such as a fluorophore, claim 1 remains unpredictable since the problem of steric hindrance prevents

complete labeling and it is unclear how the non-extrinisically labeled units of the polymer are detected.

Regarding the practice of the method generally, including the process of FRET or simply fluorescence quenching labeling of individual nucleotides and providing information about adjacent linked units, the prior art does not teach any examples where this method has been implemented successfully. The closest art, Braslavsky et al. (PNAS, 2003, vol. 100, no. 7, p. 3690-3694), teaches "repeated incorporation of fluorescently labeled nucleotides into individual DNA strands with single base resolution, allowing the determination of sequence fingerprints up to 5 bp in length (Abstract). While Braslavsky provides single base resolution, even this example had to overcome a "confounding factor in previous attempts to sequence single DNA molecules" which has been "an inability to control background fluorescence and fluorescent impurities. Braslavsky overcame this limitation by using "a combination of evanescent wave microscopy and single pair fluorescence resonance energy transfer (spFRET; refs 24-26) to reject unwanted noise" (p. 3960, col. 1-2). While this is evidence that single base resolution using FRET can be accomplished, this effort does not provide the information of single linked units that are previously labeled and instead reads the sequence as each individual nucleotide is incorporated into a template molecule (Figures 3 and 5).

Currently, the state of the art even after the filing of the instant application appears to be at the point where single molecules can be transported and detected at the single molecule level. Details such as length, strandedness, conformation, heterogeneity and some sequence information can be established (p. 580-585 of Rhee), however obtaining sequence information at the individual linked unit level, particularly along the entire length of a polymer such as nucleic

acids or polypeptides appears highly unpredictable. Rhee et al. (Trends in Biotechnology, 2006, vol. 24, no. 12, p. 580-586) states "Protein or synthetic nanopores have been used to detect DNA or RNA molecules. Although none of the technologies to date has shown single-base resolution for de novo sequencing, there have been several reports of α-hemolysin protein nanonpores being used for basic DNA analysis" (Abstract).

Therefore, the current state of the art demonstrates that providing a 'signal generating unit' for each individual unit of a polymer, nucleic acid particularly, would be subject to a high degree of unpredictability. Furthermore, regarding the practice of the invention wherein the station is embedded within a nanochannel, the current state of the art suggests a high degree of unpredictability and potentially a lack of function as applies to the method of claim 1.

Working Examples

The specification has no working examples.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus considering the breadth of the claims, as encompassing the analysis of any type of polymer, requiring that the individual units within a polymer be labeled with a light emissive compound or with an 'intrinsic' label, and considering that the method of the invention is found in an art whose nature is identified as unpredictable, the unpredictability of that art, the large

quantity of research required to define unpredictable variables, the lack of guidance provided in the specification, the presence of no working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Response to Arguments

3. Applicant's arguments filed April 23, 2007 have been fully considered but they are not persuasive.

Applicant's arguments with respect to claims 1-2, 115-122, 124, 130-156, 161-164 have been considered but are moot in view of the new ground(s) of rejection under 35 U.S.C. 112, 1st paragraph scope of enablement.

Applicant traverses the rejection of claims 1-2, 147 and 148 under 35 U.S.C. 112, 1st paragraph. Applicant asserts "the rejected claims do not require extrinsic labeling of units, nor do they require signal detection from all units in the polymer. Rather the claims embrace detecting extrinsic and/or inherent signals from at least one individual unit". Applicant also asserts that the statement cited in the 'quantity of experimentation' section of the rejection as made by Chan "refers to nanopore sequencing technology which as defined on page 30 first column of the same reference involves discrimination of individual nucleotides by nucleotide-specific ion conductance signals" and further notes that claims 1 and 147 have been amended to recite "non-ion conductance signals" (p. 13 of remarks).

Applicant asserts again, regarding the unpredictability of the art, "the claims can be performed using inherent properties of polymer units, and without signal detection from each and every unit in a polymer" (p. 13 of remarks).

These arguments regarding claims 1-2 and 147-148 are not persuasive. As noted in the amended enablement rejection stated above, the post-filing Chan reference remains relevant to the practice of the invention as claimed. While Applicant has amended the claims to read specifically on signals that are 'non-ion conductance' signals and Chan is referring to solid-state nanopores useful in sequencing with detection of ionic conductance, without evidence that FRET-labeled, fluorescence based detection practiced through a nanochannel is successful in characterizing a nucleic acid or protein polymer, the teachings of the post-filing reference remain applicable.

The enablement rejection has been adjusted to incorporate additional claims and to address additional features of the invention as claimed which are not provided with an enabling disclosure which were not included in the previous rejection. Particular concerns addressed are directed to the lack of teaching regarding the specific practice of the invention for polymers that are not nucleic acids or proteins. The specification also lacks specific teaching as to how to detect intrinsic labels in interaction with specific agents for any polymers except nucleic acids and even for nucleic acids, it is not clear from the teaching of the specification how to translate the disclosure to a functional apparatus for the practice of the method.

Conclusion

All claims stand rejected. No claims are allowed.

Claims 1-2, 115-122, 124, 130-156, 161-164 are free of the prior art, but stand rejected for other reasons.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephanie K Mummert, Ph.D.
Examiner
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SKM

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